Journal of the American College of Cardiology Vol. 45, No. 8, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.02.034

EDITORIAL COMMENT

The Use of Anti-Inflammatory Analgesics in the Patient With Cardiovascular Disease

What a Pain*

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"One of the first duties of the physician is to educate the masses not to take medicine"

—Sir William Osler (1)

With all of the recent news in both the medical and lay press regarding the use of pain relievers and cardiovascular risk, a number of questions appropriately have been raised by both patients and physicians. In particular, what can be done for the patient who already has, or is at high risk for, atherosclerotic cardiovascular disease but who also suffers from chronic, or even just intermittent, joint aches and pains? The magnitude of this problem can easily be underestimated by the busy cardiologist focusing on a patient's cardiovascular symptoms and risks during office visits, but cross-sectional studies tell us that among adults age 50 years or older, the four-week prevalence of pain is 72.4%, with 38.1% of all individuals reporting pain severe enough to interfere with daily activities (2). Therefore, any possibility of a harmful interaction between pain relievers and the atherosclerotic process, or the medicines used to prevent its complications, could have a potentially enormous impact on cardiovascular risk.

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Although the selective cyclooxygenase (COX)-2 inhibitors have been the subjects of most recent attention, nonselective COX inhibitors have been recognized for several years now as potentially limiting the cardioprotective effects of aspirin. In the initial landmark study, Catella-Lawson et al. (3) demonstrated that when the nonselective COX inhibitor ibuprofen was taken before aspirin, aspirin's ability to inhibit serum thromboxane $(TX)B_2$ formation and platelet aggregation was prevented. Acetaminophen, diclofenac, and rofecoxib did not share this effect. The postulated mechanism behind this interaction is that ibuprofen, when taken before aspirin, blocks the platelet COX-1 catalytic site and, therefore, prevents aspirin from accessing the enzyme and irreversibly acetylating the serine residue at position 529. Normally, when aspirin is able to acetylate platelet COX-1, the enzyme is inhibited for the life of the platelet. In contrast, ibuprofen, a reversible, competitive COX inhibitor, is only able to inhibit COX-1 for several hours, and by 6 h thromboxane production returns and platelet aggregation begins to approach normal levels. Because aspirin has a very short plasma half-life of only 15 to 20 min (4,5), if acetylation of COX-1 is prevented by ibuprofen during this time, acetylation cannot occur and platelet function will return to normal as soon as ~20% of platelet COX-1 activity returns (6).

Results of this trial led to a relatively specific focus on the potentially harmful interaction between ibuprofen and aspirin. Other commonly used, reversible, nonselective COX inhibitors, such as indomethacin and naproxen, were not evaluated in this study, and although there was no reason to believe that their effect on platelet COX-1 would be any different than that of ibuprofen, for many, a lack of evidence for harm translated into evidence of a lack of harm. Several clinical trials suggesting a cardioprotective effect of naproxen, in particular the widely promoted Vioxx Gastrointestinal Outcomes Research (VIGOR) trial results (7), seemed to support this view. Although conclusive evidence of any benefit or harm is still lacking, it would be fair to say that the majority of primary observational data seemed to favor a cardioprotective effect of naproxen (8), that is, until just recently, when the National Institutes of Health announced the suspension of the 2,400-patient Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) after three years due to a significant increase (no event rates have been officially released) in cardiovascular and cerebrovascular events in patients randomly assigned to naproxen compared with placebo. This widely publicized announcement has lead to even more confusion regarding the role of naproxen in particular, and pain relievers in general, in patients at risk for cardiovascular disease.

The study reported by Capone et al. (9) in this issue of the *Journal* helps shed some light on the possibility of an interaction between naproxen and aspirin therapy and mechanisms on how it might influence cardiovascular events. First, they confirmed in vitro that naproxen reversibly and competitively inhibited COX-1, that this inhibition could be overcome by increasing concentrations of arachidonic acid (AA), and that aspirin was prevented from inhibiting COX-1 in platelets pretreated with naproxen. Second, they found that when single doses of naproxen and aspirin were given simultaneously, irreversible, long-lasting inhibition of TXB_2 and AA-induced platelet aggregation by aspirin was prevented. However, and in contrast to previous results with ibuprofen, chronic administration of naproxen and aspirin simultaneously, irrespective of whether naproxen was taken before or after aspirin, provided similar and complete inhibition of serum TXB_2 production, AA-

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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Table 1. Treatment Options to Minimize Interference With Cardioprotective Effects of Aspirin in the Patient Requiring Short- or Long-Term Anti-Inflammatory Therapy

1. Consider acetaminophen, diclofenac, or COX-2 inhibitors.
2. Take a non-enteric coated aspirin at least 15 to 30 min (if chewed) or 2 h (if swallowed) prior to taking a NSAID, and at least 6 to 8 h after last dose of ibuprofen or 36 to 48 h after naproxen.
3. Consider increasing aspirin to anti-inflammatory doses (325 mg four times daily).
4. Recommend the shortest treatment course possible.

COX = cyclooxygenase; NSAID = non-steroidal anti-inflammatory drug.

induced platelet aggregation, and urinary thromboxane metabolite levels for as long as 26 h after the last aspirin dose and 12 h after the last naproxen dose. Finally, they confirmed that 100 mg of aspirin daily had no effect on COX-2-dependent prostaglandin E_2 production, whereas 500 mg of naproxen twice a day profoundly inhibited it.

The fact that chronic, concomitant naproxen and aspirin therapy did not negatively influence platelet COX activity may seem contrary to the previous results with ibuprofen and suggest a different effect of naproxen, but this finding actually is explained by the 14-h plasma half-life of naproxen compared with the only 2-h half-life of ibuprofen (10). Previous studies by this same group have found that naproxen can near maximally inhibit platelet COX-1 activity for ~24 h, by which time it starts to slowly recover (11). So does this mean that if a patient takes naproxen 500 mg twice daily, every day, that they will derive similar cardioprotection as that afforded by daily aspirin therapy? Possibly, but there are several reasons this may not be the case. First, high levels of AA can overwhelm the ability of naproxen, but not aspirin, to inhibit platelet COX-1. Theoretically, local concentrations of AA at the site of vascular injury could be high enough to displace naproxen from the enzyme leading to the generation of TXA_2. Second, as shown in this and previous studies (11), naproxen, but not aspirin, inhibits COX-2 activity and the biosynthesis of prostaglandin I_2, which is both a vasodilator and platelet inhibitor. The clinical implications of these differences are unknown but highlight that naproxen and aspirin are clearly not interchangeable therapies.

So what should we tell our patients who are undergoing chronic low-dose aspirin therapy for cardioprotection and require treatment with an anti-inflammatory analgesic? Several options are listed in Table 1, but each has its limitations. Unfortunately, only if and when adequately powered clinical trials are conducted to establish the cardiovascular risks and benefits of available pain relievers will we be able to accurately guide our patients as to what pain reliever is safest for them to take.

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